Mechanisms underlying insulin resistance in patients with pulmonary arterial hypertension. The role of bone morphogenetic protein receptor type 2 and peroxisome proliferator–activated receptor-γ in adipose tissue.

Reasons for choosing the research topic:

Pulmonary arterial hypertension (PAH) is a severe and incurable disease. It leads to decreased life expectancy and quality. It results from narrowing and obliteration of small pulmonary arteries, which leads to increase of pulmonary artery pressure and heart failure. The main symptoms include progressing dyspnea and limitation of functional capacity. Idiopathic PAH (IPAH) may be diagnosed in patients with PAH without a positive family history and predisposing factors for PAH such as congenital heart defect, systemic sclerosis, portal hypertension, HIV infection, use of appetite suppressant drugs. In case of detecting mutation in PAH-predisposing gene a patient is diagnosed as heritable PAH (HPAH). Mutation in BMPR2 gene is responsible for most of HPAH cases. Factors predisposing to development of PAH still remain unclear, however recent experimental studies indicate the role of metabolic alterations of adipose tissue (including insulin resistance). Our preliminary data indicate that IPAH patients have altered lipid profile and higher prevalence of insulin resistance, when compared to healthy subjects. These metabolic alterations are associated with disease severity and prognosis in PAH patients but their underlying mechanism is not known. Recently, an important role in pathogenesis of PAH has been assigned to the particles involved in regulation of development and metabolism of adipose tissue such as bone morphogenic protein receptor type 2 (BMPR2), peroxisome proliferator–activated receptor-γ (PPAR-γ) and adipokines. In experimental studies in animal models these particles were able to influence pulmonary vascular remodeling. For this reason PAH has been recently considered as a systemic disease. Animals with inactivated BMPR2 gene had decreased PPARγ activity and disturbed secretion of adipokines. This resulted in both pulmonary hypertension and insulin resistance. In the experimental studies these alterations were reversible by PPARγ agonists, thiazolidinediones.

The proposed study will allow not only to expand the current knowledge on PAH but also may result in further research on the role of thiazolidinediones in the treatment of patients with PAH.

Objective of the project: To assess whether altered BMPR2 and PPAR-γ signaling influence adipose tissue function including its role in insulin resistance and synthesis of adipokines.

Research to be carried out:

Study group (n=60): patients ≥18 years old diagnosed with IPAH or HPAH (de novo or previously). Patients with diabetes or taking antidiabetic drugs will be excluded. Based on hyperinsulinemic–euglycemic clamp test patients will be qualified as insulin resistant or sensitive. The amount of adipose tissue (anthropometric measures) and standard cardiovascular risk factors including smoking and sedentary life style will be assessed in each patient. Patients and their first degree relatives (preferably parents) will undergo exome sequencing to find mutations in PAH-predisposing genes (including BMPR2 gene) and also to find other gene variants which can influence BMPR2 and PPAR-γ signaling. Adipocytes will be obtained from deep layer of subcutaneous adipose tissue by the large bore needle biopsy. Assessment of adipose tissue function will include analysis of adipocyte proteome and transciptome, adipocyte levels of BMPR2 and PPAR-γ and adipocyte and plasma levels of adipokines (adiponectin, leptin, resistin, omentin, visfatin, apelin, grelin, IL-1β, IL-6, TNF-α). To confirm the role of reduced BMPR2 and PPAR-γ expression in adipocyte function of PAH patients we will do additional in vitro experiments. Adipose tissue fragments will be cultured with TNF-α to mimic in vitro a proinflammatory environment of PAH and to better discriminate between BMPR2 mutation carriers and non-carriers. Then adipocytes will be supplemented with BMP or with pioglitazone to assess whether restoration of BMP2 and PPAR-γ signaling ameliorates the effects of TNF-α. During in vitro experiments we will measure adipose tissue function with the same methods as listed above. Standard markers of pulmonary hypertension severity will be assessed in all patients and will be referred to insulin resistance, and adipose tissue function including BMPR2 and PPAR-γ signaling.